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Neuropsychological performance in frontal lobe epilepsy

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The search for a special neuropsychological profile of frontal lobe epilepsy subjects (FLE) has so far led to inconclusive results. In this paper we compared the preoperative neuropsychological performance of FLE and temporal lobe epilepsy (TLE) subjects. We further investigated whether frontal lobe lesions of epileptogenic cause produce the same type of cognitive dysfunction as do tumours of the frontal lobe. Sixteen FLE subjects were compared to 16 TLE subjects as well as to a group of 10 subjects after the removal of frontal lobe tumors (TUM) and a healthy control group. A set of neuropsychological test measures routinely used for presurgical evaluation, an emotional conceptualization task and two associative learning tasks were administered. We found that subjects with frontal lobe damage were significantly impaired relative to controls on a wide range of cognitive functions independent of neurological cause. FLE subjects could hardly be discriminated from TLE subjects as both groups showed a similarly reduced level of neuropsychological performance. Our results demonstrate the devastating effect that frontal lobe epilepsy can have on cognitive functioning. Routinely used neuropsychological test measures lack the specificity to distinguish between frontal and temporal lobe epilepsy. Highly specialized measures are necessary to reveal differences.

Key words: frontal lobe epilepsy; neuropsychological deficits; associative learning; epilepsy; cognitive performance.

INTRODUCTION

The assessment of neuropsychological function is now an established part of the evaluation of subjects with intractable epileptic seizures. One aim of neuropsychological testing in epilepsy has always been to distinguish between subjects with epileptogenic foci in different parts of the brain. Today a large body of evidence exists on the special neuropsychological deficits that regularly accompany temporal lobe epilepsy (TLE)[1–4]. In contrast, the neuropsychological profile of subjects with frontal lobe epilepsy (FLE) has proved much harder to characterize. Only a limited number of studies has systematically looked into the neuropsychological consequences of frontal lobe epilepsy independent of surgical lesions and results to date are far from conclusive[5–8].

Delaney *et al.*[6] studied the performance of TLE and FLE subjects on a set of memory tests. He found that memory function in TLE subjects was impaired relative to controls and to FLE subjects whereas FLE subjects did not differ from healthy controls in their memory performance. However, Kemper *et al.*[9] found memory deficits in subjects with FLE that could hardly be differentiated from those observed in subjects with TLE. Helmstaedter *et al.*[7] could identify a number of neuropsychological test measures that revealed significant differences between TLE and FLE subjects. In their investigation FLE subjects performed significantly below TLE subjects on measures of attention, speed, motor co-ordination and a set of functions such as response inhibition, concept formation and fluency which are typically seen as 'frontal lobe functions'. Using different measures but again focussing on typical frontal type pathology Upton & Thompson[8] found that FLE subjects showed impaired executive skills in some of the applied test measures (e.g. cost estimation, Stroop interference task) relative to TLE subjects and thus demonstrated a pattern of results similar

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to that described after other types of frontal lobe lesions. However, the most widely used test measure of frontal type deficits, the Wisconsin card sorting test (WCST), did not reveal any differences between FLE and TLE subjects in this study. There is evidence that the performance of TLE subjects in the WCST is also suggestive of frontal-lobe-pathology, i.e. a high number of perseverative errors[10,11]. In evaluating subjects with epilepsy as much as those with other types of neurological pathology poor performance in the WCST may therefore not be a reliable sign of frontal lobe lesions[12].

In summary, in three group studies some neuropsychological tests could show significant differences between FLE and TLE subjects. The available evidence so far suggests that FLE subjects show memory deficits to a lesser degree than TLE subjects and more deficits in tests that have already been proved to be sensitive to frontal lobe dysfunction of other than epileptogenic type, i.e. executive and motor skills. However, there is a considerable overlap of impaired functions in both groups with FLE subjects showing 'temporal type' impairment, i.e. memory deficits and TLE subjects showing 'frontal type' impairment, i.e. a high number of perseverative errors in the WCST. Thus, selected test measures are necessary to reveal differences between groups. This fact may create the difficulty, as some authors have pointed out, that it remains unclear whether statistically significant differences between large patient samples on highly selected experimental measures are of any clinical relevance[8].

The difficulties to consistently distinguish between FLE and TLE subjects may have different causes: first, EEG monitoring in FLE and TLE subjects frequently shows widespread propagation of epileptic activity towards other brain areas ipsilaterally and contralaterally[13,14]. Especially in frontal lobe epilepsy seizure spread has been shown to be extremely rapid[15]. Second, the frontal lobes are the largest of all cortical lobes and hold numerous connections to other brain areas. Pathways linking the frontal lobes with the temporal lobes have been described[16] and may be the route by which seizure activity in frontal areas can disturb the functional integrity of distant brain regions in the temporal lobe and the other way round. Third, many neuropsychological test measures that are in constant use today and which are considered indicators of focal brain damage may in fact lack the specificity and sensitivity which is attributed to them, e.g. the Wisconsin card sorting test[17].

In the present study we wanted to compare preoperative performance of TLE and FLE subjects on a set of neuropsychological test measures routinely used for presurgical evaluation. We wished to establish the capability of these tests to distinguish between subjects with frontal lobe epilepsy and those with temporal lobe epilepsy. Additionally a task for studying the conceptualization of emotional facial expressions[18] and two newly designed associative learning tasks thought to reveal special learning and memory problems of subjects with temporal lobe epilepsy[19] were administered. We hypothesized, that FLE subjects would show 'frontal lobe type' deficits, i.e. a high number of perseverative errors in the *Wisconsin card sorting test* and a high number of sorting errors in the *emotional conceptualization task*, low short-term memory capacity and working memory problems. TLE subjects were expected to score lower than FLE subjects and normal controls on declarative memory tasks. As the amygdala was affected in most TLE subjects after surgery they were predicted to have more problems with learning emotional facial expressions than neutral facial identities in our newly designed experimental tasks. In a second study we set out to investigate whether subjects with frontal lobe epilepsy present with the same type of cognitive dysfunction as do subjects with focal frontal lesions of other causes, i.e. tumours.

STUDY I

METHOD

Subjects

The two study groups consisted of subjects with either frontal lobe epilepsy (FLE, $n = 16$) or temporal lobe epilepsy (TLE, $n = 16$). All subjects were regularly seen as outpatients at the specialized epilepsy clinic of the Department of Clinical Neurophysiology. Classification of epilepsy subjects (consensus diagnosis) was based on repeated EEG monitoring (non-invasive EEG recordings of interictal epileptiform discharges), seizure semiology, clinical history and cortical imaging (MRI). All TLE subjects underwent long-term video-EEG telemetry and in some cases single photon emission CT (SPECT) as part of the presurgical evaluation. Six subjects with FLE received long-term video-EEG telemetry as well and in one FLE subject invasive EEG recordings were used to support the diagnosis of frontal lobe epilepsy. Severity of illness was rated according to the scoring system of Engel *et al.*[20] which is based on frequency and impact of seizures.

Subjects with frontal lobe epilepsy (FLE)

There were different causes of epilepsy in the FLE group. In three subjects seizures started after traumatic brain injury (grade I $n = 1$, grade III $n = 2$). Four

Table 1: Study I: Demographic and clinical characteristics.

Characteristic	Frontal epilepsy (FLE) ($n = 16$) M	SD	Temporal epilepsy (TLE) ($n = 16$) M	SD	Controls (CG) ($n = 15$) M	SD
Age (years)	41	14	34	7	42	13
Education (years)	12	2	12	1	13	1
Age at seizures onset (years)	27	16	8[d]	7	—	—
Duration of illness (years)	14	13	26[d]	11	—	—
Severity of illness[a]						
1st assessment[b]	5	3	8[d]	0	—	—
2nd assessment[c]	—	—	4[e]	2	—	—
Sex (F : M)	9 : 7		8 : 8		11 : 4	

[a] As determined by Engel *et al.*[20] Higher scores imply greater severity of seizures. [b] FLE subjects were only tested once. First assessment of TLE subjects took place as part of the presurgical evaluation. [c] Second assessment of TLE subjects took place about 12 days after surgery. [d] Significantly different (*U* test; $P < 0.05$) from group FLE. [e] Significantly different (Wilcoxon test; $P < 0.05$) from preoperative value.

subjects experienced frontal lobe seizures because of other MRI identifiable lesions of the frontal lobe (meningioma, oligodendroglioma, abscess or angioma, respectively). These four subjects were surgically treated but seizures did not cease afterwards. The remaining nine FLE subjects had epilepsy of an unknown aetiology. One of those had a venous malformation and one showed lesions because of tubercular sclerosis but it remained unclear whether these pathologies accounted for seizures. In 11 FLE subjects the epileptic focus could be localized to the left frontal lobe and in five subjects to the right frontal lobe. All FLE subjects were on anticonvulsant medication.

Subjects with temporal lobe epilepsy (TLE)

TLE subjects were all pharmacoresistent and therefore scheduled for neurosurgery to remove the epileptogenic focus. Subjects were administered a neuropsychological test battery before surgery as part of extensive presurgical assessment and were then re-evaluated again about 12 days postoperatively when they performed some of the neuropsychological tests again and in addition two experimental learning tasks. Presurgical MRI scanning showed structural lesions of the temporal lobe in most subjects such as hippocampal sclerosis ($n = 12$), ganglioglioma ($n = 1$), hamartia ($n = 4$), gliosis ($n = 1$) or venous malformation ($n = 2$). Ten subjects had left temporal lobe epilepsy and were therefore operated on the left side and six subjects suffered from right temporal lobe epilepsy and were operated on the right side. Three subjects underwent selective amygdalohippocampectomy with removal of the amygdala and the anterior part of the hippocampus. Thirteen subjects had an anterior temporal lobectomy with part removal of the temporal pole and the anterior hippocampus and complete or nearly complete removal of the amygdala. Analysis of postsurgical MR scans showed complete unilateral amygdala removal in four subjects, the remaining 12 subjects had substantial but incomplete amygdala damage. Pre- and postsurgical medication remained unchanged.

TLE subjects matched FLE subjects well in terms of age, gender and years of education (cf. Table 1). Age of seizure onset was significantly lower and thus duration of illness significantly longer in TLE subjects. Before surgery TLE subjects suffered from significantly more frequent and more disabling seizures than FLE subjects and thus attained higher scores on the scoring sytems for seizure frequency of Engel *et al.*[20]. However, their condition improved significantly after surgery and thus severity of illness in TLE subjects no longer differed from FLE subjects.

Control subjects

The epilepsy subjects were compared with 15 healthy control subjects recruited for the study by an advert in a local newspaper. Control subjects were paid for their participation and matched the epilepsy subjects in terms of age and years of education.

After complete description of the study to the subjects informed consent was obtained.

Neuropsychological testing

We chose a set of neuropsychological test measures that are routinely used for presurgical evaluation and for which age adjusted normative data is available. The following tests were administered according to standard procedures to all epilepsy subjects and control subjects: using the German version of the *Wechsler adult intelligence scale-revised (WAIS-R)*, measures of full scale IQ, verbal IQ and performance IQ were derived using a short form which comprised

the subtests *information, similarities, block design and picture completion*. These subtests were chosen because they show high correlation with full scale IQ[21,22]. Mnemonic functions were assessed with subtests of a German translation of the *Wechsler memory scale-revised (WMS-R)*[23]. For testing attentional performance and psychomotor speed, the *trail making test* (parts A and B) was used[24]. Visuospatial processing of faces was evaluated using the *facial recognition test (BFRT)* of Benton[25]. The *Wisconsin card sorting test (WCST)* was administered to TLE and FLE subjects to study impairment of abstract conceptualization and shifting ability[26]. For technical reasons the control group did not receive this test.

Emotional conceptualization task

Deficits on measures of concept formation have long been associated with frontal lobe pathology[27]. We used a sorting task to study the conceptualization of emotional facial expressions[18]. Sixteen pictures of the Ekman series[28] representing facial expressions of prototypic emotions were presented to the subject. The stimulus set contained two pictures each of four frequently-experienced negative emotions (anger, fear, disgust and sadness), two pictures of faces expressing surprise, and a pair of neutral, unemotional faces. To balance the number of negative emotions shown we included four pictures representing joy: two pictures showing faces expressing high intensity joy (joy) and two showing a lower intensity of joy (pleasure). Each pair of identical facial expressions contained one picture of a female face and one of a male face expressing the emotion in question. All pictures used yielded highly consistent judgements by a control group[28]. Subjects were asked to sort those pictures which showed identical emotional facial expressions into groups. There was no restriction as to the number of groups which could be formed or the number of pictures to sort into one group. The correct solution of the task was to sort the eight pairs of identical expressions into eight different groups. Because joy and pleasure represent different intensities of the same emotion sorting these two pairs in only one group was also regarded as a correct solution.

Performance in the sorting task was judged according to the number of sorting errors. We calculated three different types of errors: first, the coordination error, which indicated the number of pairs of identical emotional facial expressions not sorted into the same group; second, the differentiation error, which showed the number of non-identical emotional expressions sorted into the same group; third the sum of errors, which indicated the total number of errors in the individual sorting matrix.

Associative learning tasks

In order to assess associative learning of facial identities and emotional facial expressions two different experimental designs were developed[19].

Both associative learning tasks used pictures of the Ekman and Friesen series[28]. This series contains pictures of basic facial emotions and also provides reliability ratings regarding the emotion expressed. Only pictures with high reliability rating scores were chosen (ranging from 79 to 100 percent). The first task comprised neutral facial expressions (*identity learning task*), the second task used the same faces showing emotional expressions (*emotion learning task*). Both tasks were similarly structured to match task demands. The *identity learning task* was always given first to prevent subjects from learning the identities during the *emotion learning task*. Subjects got a written and an oral instruction. Pictures were presented as slides by using a PC-driven tachistoscope. There was always a time lag of at least 20 minutes between the two tasks filled with other tests.

Associative learning of facial identities (*identity learning task*)

The task comprised six learning and six recall trials. In the learning trial, six pairs of faces showing neutral facial expressions were presented for 2 seconds each. The total of 12 pictures used consisted of six male and six female faces. In the recall trial, only one face of each pair was presented at a time, and the subject had to select the matching face out of six photographs on the table. There was no time limit for selection. The examiner gave feedback as to whether the answer was right or wrong but did not point out the correct face in the case of a wrong answer. The experiment was discontinued if the subject answered all six pairs correctly or after the completion of six learning and recall trials. In each trial, pairs were presented in a different order.

Associative learning of emotional facial expressions (*emotion learning task*)

The combinations of faces used were the same as in the *identity learning task*. But this time all faces showed one of the six basic emotional expressions (anger, fear, happiness, surprise, disgust, and sadness). All combinations consisted of two different emotions. Thus, each emotional expression was used twice. Pair 1 consisted of the emotions anger–happiness, pair 2: sadness–fear, pair 3: happiness–surprise, pair 4:

disgust–sadness, pair 5: surprise–disgust, pair 6: fear–anger. Pairs 1, 2 and 5 showed male faces, pairs 3, 4, and 6 female faces. Pairs were presented for 3 seconds each. Ten learning and recall trials were administered to account for the greater difficulty of the task. In the recall trial, again only one picture of each pair was presented and subjects had to select the matching emotion out of six schematic drawings of emotional facial expressions on the table. In order to avoid confusion about the correct verbal description of emotions subjects were required to point to the schematic faces indicating the emotion of the missing face. There was no time limit for selection and feedback about the correctness of the answer was given by the experimenter. Again the task was discontinued if all six emotions were matched correctly, or after 10 learning and recall trials had been completed. Afterwards subjects were asked to name each of the six schematic emotions.

Performance in both associative learning tasks was measured by the total number of correctly recalled pairs over all trials (total recall, sum). If subjects reached the learning criterion of six correct answers before all trials were finished the task was discontinued and all further trials were counted as fully accomplished. If subjects broke off the test because of other reasons (e.g. lack of motivation or concentration) the number of correct answers in the last completed trial was assumed for the missing trials. The maximum number of correct answers per trial was six in both associative learning tasks. The maximum total score in the *identity learning task* and in the *emotion learning task* was 36 and 60, respectively. To compare both scores the percentage of correctly recalled pairs over all trials was used (percent total recall).

Statistical analysis

Statistical computations were based on scaled scores (WAIS-R) or raw scores. Because of the small number of subjects in each group, only non-parametric statistical methods were used (Kruskal–Wallis 1-way ANOVA, Wilcoxon test, Mann–Whitney *U* test, Spearman rank correlation). Frequencies were compared using the binomial test. All analyses were two-tailed and the alpha was defined at 0.05. In order to minimize the statistical type II error, Alpha corrections were only applied for neuropsychological measurements being obviously dependent (i.e. measures of the WCST). All statistical comparisons were performed using the Statistical Package for the Social Sciences (SPSS for Windows, Version 6.0.1).

It should be mentioned that due to our sample sizes and the non-parametric testing procedures the power of our tests might have been limited. However, according to diagnostic experience group differences of about one-third to one-half of standard deviation units should be seen as clinically relevant. Aiming at group differences of this magnitude the sample size of 16 subjects in each group accounted for a statistical power of 0.80 and was therefore sufficient to detect clinically relevant differences.

RESULTS

Neuropsychological testing

The neuropsychological test results of FLE and TLE subjects and control subjects are summarized in Table 2. For TLE subjects preoperative values are reported. Postoperative values were subjected to the same analyses. However, postoperative performance of TLE subjects remained largely the same and no additional significant differences between the groups emerged.

Significant group differences (Kruskal–Wallis) occurred on verbal, performance and full scale IQ. *Post hoc* analyses revealed that control subjects scored significantly higher than FLE subjects and TLE subjects. Full scale IQ was below or very low average in most epilepsy subjects with about 60% of FLE and about 50% of TLE subjects performing below the 16th percentile. However, no significant differences were found between FLE and TLE subjects.

Regarding memory performance significant group differences were seen for four of the eight *Wechsler memory scale* subtests (cf. Table 2). Normal control subjects performed significantly better than FLE subjects on *digit span forward* and scored well above FLE and TLE subjects on *digit span backward, logical memory, immediate recall, logical memory, delayed recall* and *visual reproduction, delayed recall*. No significant differences occurred between the FLE and TLE group except for *digit span forward* where TLE subjects showed a significantly better performance than FLE subjects.

Significant group differences were found in both parts of the *trail making test* with epilepsy subjects in the FLE and TLE group performing significantly slower than control subjects.

Both epilepsy groups showed marked difficulties in the *Wisconsin card sorting test* with about 60% of subjects in the FLE group and in the TLE group scoring below the 16th percentile. However, no significant group differences became apparent between the FLE and the TLE group.

There were no significant group differences for the number of correct responses on the *Benton facial recognition test* and almost all subjects in all three groups scored well within the normal range.

Table 2: Study I: Neuropsychological test performance.

Test	Frontal epilepsy (FLE) ($n = 16$) M	SD	Temporal epilepsy (TLE) ($n = 16$)[a] M	SD	Controls (CG) ($n = 15$) M	SD
WAIS-R						
Verbal IQ	81	16	81	14	114[c,d]	17
Performance IQ	90	22	94	14	116[c,d]	21
Full scale IQ	84	20	85	14	117[c,d]	16
WMS-R (percentiles)						
Digit span fwd	13	13	35[e]	32	54[c,d]	24
Digit span bwd	24	23	39	26	66[c,d]	22
Visual memory span fwd	42	32	54	28	59	29
Visual memory span bwd	49	30	57	27	71	27
Logical memory I	37	31	33	28	58[c,d]	29
Logical memory II	28	26	24	22	52[c,d]	27
Visual reproduction I	65	29	65	32	82	22
Visual reproduction II	53	38	34	25	84[c,d]	16
Trail making (percentiles)						
Part A	50	28	57	29	85[c,d]	17
Part B	45	39	60	23	87[c,d]	11
WCST (percentiles)[b]						
Categories achieved	10	6	9	5	—	—
Total errors	15	25	20	29	—	—
Perseverative errors	21	29	22	33	—	—
Benton facial recognition (percentiles)	49	31	49	31	68	25

[a] Values were taken from preoperative testing. [b] The control group did not receive the WCST. [c] Significant group difference (Kruskal–Wallis; $P < 0.05$). [d] Significantly different (U test; $P < 0.05$) from group FLE and TLE. [e] Significantly different (U test; $P < 0.05$) from group FLE.

Emotional conceptualization task

Mean numbers of errors and standard deviations of FLE and TLE subjects and control subjects in the *emotional conceptualization task* are summarized in Table 3. Significant group differences (Kruskal–Wallis, $P < 0.05$) occurred for the number of differentiation errors and the sum of errors. For both error types *post hoc* analyses (U tests) revealed that both the FLE and TLE subjects had made significantly more errors than control subjects. No significant differences were found between the TLE and the FLE group.

Associative learning tasks

In the *identity learning task* significant group differences (Kruskal–Wallis) were found between the three groups for the total number of recalled pairs. *Post hoc* analyses (U tests) revealed that controls had recalled significantly more correct pairs of faces than FLE subjects. No differences were found between the TLE group and controls and between the two epilepsy groups for the total number of recalled pairs. There were, however, significant group differences between TLE and FLE subjects on the number of recalled items in the third and sixth block, with FLE subjects performing below TLE subjects (cf. Fig. 1).

In the *emotion learning task* again significant group differences between the three groups occurred for the total number of correctly recalled pairs (cf. Table 4 and Fig. 2). *Post hoc* analyses showed that in this task both FLE and TLE subjects had scored significantly below control subjects. There were no significant differences between the FLE and TLE group.

Lateralization of focus

In the FLE group lateralization of the epileptic focus did not have a differential effect on test measures. In the TLE group before surgery lateralization of the focus only influenced *visual memory span backward of the Wechsler memory scale-revised*, when TLE subjects with right-sided foci scored significantly below those with left-sided foci (U test, $U = 6.0$, $P < 0.007$). After surgery TLE subjects with left-sided lesions showed significantly more difficulties in verbal learning (*logical memory II* of the *WMS-R*) than subjects with right-sided lesions (U test, $U = 8.5$, $P < 0.03$).

Table 3: Study I: Emotional conceptualization task.

	Frontal epilepsy (FLE) ($n = 15$)		Temporal epilepsy (TLE) ($n = 15$)[a]		Controls (CG) ($n = 14$)	
Error type	MD	SD	MD	SD	MD	SD
Coordination error	2.3	2.1	1.9	2.2	1.2	1.4
Differentiation error	6.5	3.1	6.8	2.8	3.6[b,c]	3.0
Sum of errors	12.6	8.1	13.9	8.5	6.4[b,c]	5.3

[a] Values were taken from preoperative testing. [b] Significant group difference (Kruskal–Wallis; $P < 0.05$). [c] Significantly different (U test; $P < 0.05$) from group FLE and TLE.

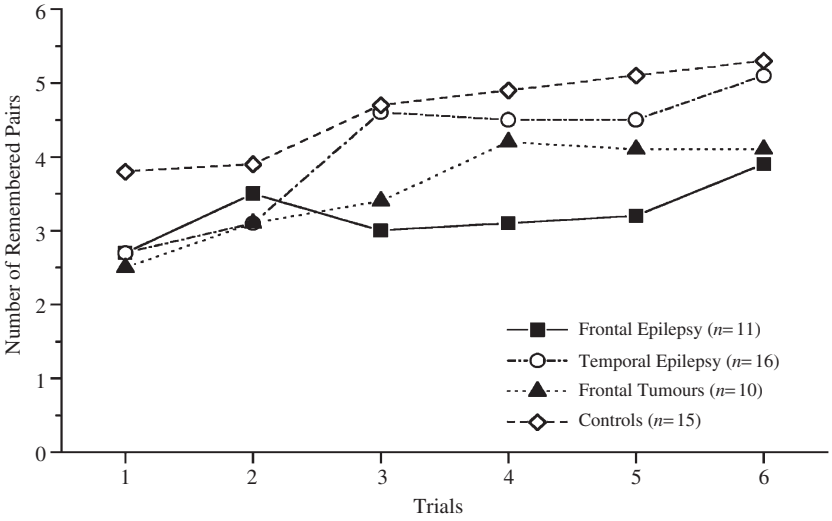

Fig. 1: Results of the identity learning task for all groups of subjects. Means of the number of correctly remembered pairs are given for the six trials administered in this task.

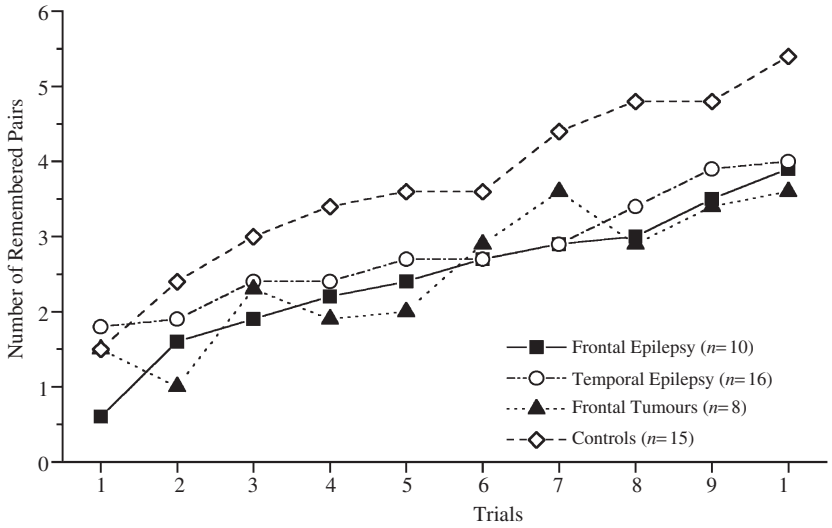

Fig. 2: Results of the emotion learning task for all groups of subjects. Means of the number of correctly remembered pairs are given for the 10 trials administered in this task.

Table 4: Study I: Associative learning tasks.

	Frontal epilepsy (FLE) ($n = 11$)[a]		Temporal epilepsy (TLE) ($n = 16$)[b]		Controls (CG) ($n = 15$)	
Total score (% correct)	MD	SD	MD	SD	MD	SD
Identity learning task	54	20	68	21	77[c,e]	16
Emotion learning task	41	18	47	20	62[c,d]	19

[a] Only 10 subjects completed the emotion learning task. [b] Values were taken from postoperative testing. [c] Significant group difference (Kruskal–Wallis; $P < 0.05$). [d] Significantly different (U test; $P < 0.05$) from group FLE and TLE. [e] Significantly different (U test; $P < 0.05$) from group FLE.

Table 5: Study I: Influence of seizure history variables on cognitive functioning of TLE subjects (group 2).

Test	Age at seizure onset (years)[a]	Duration of illness (years)[a]	Severity of illness (preoperatively)[a,b]
WAIS			
Performance IQ	0.55*		
Similarities	0.53*		
Block design	0.57*	−0.62*	
WMS-R			
Digit span fwd	0.52*	−0.52*	
Visual memory span bwd		−0.61*	
Logical memory I	0.60*		−0.54*
Logical memory II	0.76**		−0.51*
Visual reproduction I		−0.58*	
Visual reproduction II		−0.63*	
Trail making test			
Part A		0.67**	

[a] Spearman's rank correlation coefficient. [b] According to Engel *et al.*[20] * $P < 0.05$, ** $P < 0.01$.

Influence of seizure history variables on neuropsychological performance and associative learning

Spearman's rank correlations were used to examine the influence of seizure characteristics (age at start of seizures, duration of illness, severity of seizures according to Engel *et al.*[20]) on neuropsychological test performance, conceptualization of emotional facial expressions and on associative learning tasks. In the FLE group no significant correlation between seizure characteristics and performance in neuropsychological or experimental tasks was found.

However, in the TLE group age at start of seizures and duration of illness showed significant correlation with preoperative neuropsychological test parameters (cf. Table 5): the earlier seizures had started the lower the test scores attained by TLE subjects on the following measures: performance-IQ, subtests *similarities and block design* of the *WAIS-R* and *digit span forward and logical memory I* and *II* of the *WMS-R*. A longer duration of illness was significantly associated with lower test scores on *block design* of the *WAIS-R, digit span forward, visual memory span backward, visual reproduction I and II of the WMS-R* and on the *trail making test, part A*. Greater preoperative severity of seizures according to Engel *et al.*[20] resulted in significantly lower test scores on *logical memory I* and *II* of the *WMS-R*. There was no significant correlation between experimental tasks and seizure characteristics.

STUDY II

METHODS

Subjects

FLE subjects were the same as in the first study. They were compared to a group of 10 subjects (female $n = 5$, male $n = 5$) with frontal lobe tumours (TUM). Tumour subjects were significantly older than epilepsy subjects ($M = 53.1$, $SD = 12.22$; $P < 0.05$) but did not significantly differ from epilepsy subjects in terms of educational level and gender distribution. Five TUM subjects had mesodermal tumours (meningiomas), four subjects suffered from neuroepithelial tumours (astrocytomas or oligodendrogliomas) and one had metastases in the frontal cortex because of a carcinoma. In four subjects the right frontal lobe and in six subjects the left frontal lobe was affected. Subjects

were seen 10 to 12 days after surgical removal of tumours. Postsurgical assessment seemed preferable to presurgical evaluation as high intracranial pressure and oedemas before the removal of tumours usually result in unspecific global impairment.

Neuropsychological testing

Tumour subjects were administered the same neuropsychological test battery as in study I except for the *Wisconsin card sorting test*.

Associative learning tasks

Tumour subjects also performed the two associative learning tasks (*identity learning task and emotion learning task*) described earlier.

RESULTS

The neuropsychological and experimental test results of FLE and TUM subjects can be seen from Tables 6 and 7. Subjects with frontal lobe epilepsy had significantly lower performance IQ scores than subjects with frontal lobe tumours. They also had a significantly lower immediate memory span in *digit span forward* of the *WMS-R*. No further differences occurred on any other measure of intelligence, memory or attention/concentration. Furthermore, no significant differences could be found between the TUM and the FLE group on the *identity learning task and the emotion learning task*. Both groups showed a very similar level of performance (cf. also Figs 1 and 2).

DISCUSSION

Differences in associative learning between FLE and TLE subjects

Regarding the two associative learning tasks it emerged that while the FLE subjects had difficulties with both learning the associations between emotional facial expressions *and* neutral faces the TLE group showed a specific performance deficit only for associative learning of emotional facial expressions.

Whether FLE and TLE subjects differ in their performance on memory tests is still a matter of dissent and may depend upon the performance measures used. While Delaney *et al.*[6] found only TLE subjects to be impaired on a set of memory tests, Kemper *et al.*[9] also detected memory deficits in FLE subjects that could not be differentiated from those in TLE subjects. Studying FLE and TLE subjects after surgery for epilepsy, Petrides[29] showed that subjects with frontal excisions performed significantly below controls on a conditional associative learning task while TLE subjects only showed deficits if large portions of the hippocampus had been resected. It appeared that frontal lobe damaged subjects had general difficulties when the right response to a given stimulus had to be selected from different choices. Furthermore, some researchers have reported that frontal lobe damaged subjects while not presenting with a genuine memory deficit show an inability to use elaborative and organizational strategies when presented with learning and memory tasks[30, 31]. These deficits may explain the poor performance of FLE subjects in our study on both associative learning tasks. Whereas TLE subjects did not differ from controls when only identities had to be learned they performed significantly below controls and as poorly as FLE subjects when pairs of emotional facial expressions had to be recalled. Thus, in contrast to the global associative learning impairment of FLE subjects TLE subjects showed a selective deficit when learning pairs of emotional facial expressions. This special deficit is consistent with our hypotheses and may be applicable to the damage of structures that control the processing of emotional information, e.g. the amygdala[19].

Lack of differences in the neuropsychological profile of FLE and TLE subjects

Significant differences between frontal and temporal epilepsy subjects occurred just on one subtest of the *WMS-R* when FLE subjects demonstrated a significantly reduced verbal short-term memory span compared to TLE subjects on *digit span forward*. Apart from this there were no differences between the two epilepsy groups on measures of intelligence, memory and concept formation. Both groups performed on the same deficient level. These findings are only partly consistent with the literature. Measures of attention (*digit span*) have been found by different researchers to be impaired in frontal lobe damaged subjects in general[27] and may also be a suitable tool to distinguish between FLE and TLE subjects[7, 8].

We failed to find any differences in the performance of FLE and TLE subjects on measures of concept formation. Both FLE and TLE subjects demonstrated deficits when requested to categorize emotional facial expressions in the *emotional conceptualization task* and showed the same level of performance in the *Wisconsin card sorting test*. Deficits on measures of concept formation have long been associated with frontal lobe pathology[27, 32, 33]. In the investigation

Table 6: Study II: Neuropsychological test performance.

Test	Frontal epilepsy (FLE) ($n = 16$) M	SD	Frontal tumours (TUM) ($n = 10$)[a] M	SD	Controls (CG) ($n = 15$) M	SD
WAIS-R						
Verbal IQ	81	16	94	25	114[b,c]	17
Performance IQ	90	22	100[d]	11	116[b,c]	21
Full scale IQ	84	20	96	18	117[b,c]	16
WMS-R (percentiles)						
Digit span fwd	13	13	39[d]	26	54[b,d]	24
Digit span bwd	24	23	30	29	66[b,e]	22
Visual memory span fwd	42	32	52	29	59	29
Visual memory span bwd	49	30	57	23	71[b,d]	27
Logical memory I	37	31	33	30	58[b,c]	29
Logical memory II	28	26	27	18	52[b,c]	27
Visual reproduction I	65	29	52	32	82[b,e]	22
Visual reproduction II	53	38	32	26	84[b,c]	16
Trail making (percentiles)						
Part A	50	28	38	26	85[b,c]	17
Part B	45	39	51	29	87[b,c]	11
Benton facial recognition (percentiles)						
	49	31	40	32	68	25

[a] Values were taken from postoperative testing. [b] Significant group difference (Kruskal–Wallis; $P < 0.05$). [c] Significantly different (U test; $P < 0.05$) from group FLE and TUM. [d] Significantly different (U test; $P < 0.05$) from group FLE. [e] Significantly different ($P < 0.05$, Mann–Whitney U test) from group TUM.

Table 7: Study II: Associative learning tasks.

Total score (% correct)	Frontal epilepsy (FLE) ($n = 11$)[a] MD	SD	Frontal tumours (TUM) ($n = 10$)[b] MD	SD
Identity learning task	54	20	59	22
Emotion learning task	41	18	42	28

[a] Only 10 subjects completed the emotion learning task. [b] Only eight subjects completed the emotion learning task.

of Helmstaedter *et al.*[7] FLE subjects scored below TLE subjects on a measure of concept formation (visual verbal test). However, other investigators have reported that TLE subjects perform as poorly as FLE subjects on the *Wisconsin card sorting test*, a widely used measure of frontal type pathology[8,10]. In general, the sensitivity and specificity of the WCST as a measure of frontal lobe damage has been questioned[12]. The lack of differences in the neuropsychological performance of FLE and TLE subjects on the WCST and the *emotional conceptualization task*, as well as on other test measures, may be the result of widespread propagation of epileptic activity as, for instance, seizures with temporal lobe onset have been shown to spread to ipsilateral and contralateral frontal areas[13,14].

In summary while we could show differences between FLE and TLE subjects on two single measures we could not replicate the distinguishable neuropsychological profiles of the two groups that some researchers have reported with FLE subjects being mainly impaired on measures of attention, speed, motor coordination and executive functions[7,8] and TLE subjects scoring poorly on memory tasks[6]. Highly selected test measures and large sample sizes seem necessary to reveal group differences.

One potential reason for the failure to detect more differences between FLE and TLE subjects could have been that our sample of FLE subjects comprised subjects with a very heterogeneous aetiology of seizures: some had surgical lesions, some had brain concussions due to head trauma and others had no detectable structural lesions at all. Also variance in duration of illness and frequency of seizures was high. However, heterogeneity in terms of the clinical history and current severity of symptoms is an invariable

feature in all samples of FLE subjects that have been investigated so far[7,8] and may thus not account for the failure to detect differences between FLE and TLE subjects.

Another reason for the failure to detect differences might have been the sample size. However, statistical power was sufficient to detect group differences of a magnitude that is relevant for diagnostic purposes (e.g. differences between TLE and FLE subjects on *digit span*). As other researchers have done one might even doubt whether statistically significant differences between very large patient samples on highly selected measures are of any clinical relevance[8].

Because of the relatively small number of subjects in the FLE group ($n = 16$) there was no possibility to account for the differential effect that lesion site within the frontal cortex might have on cognitive performance. For instance, lesions in dorsolateral convexity have been shown to have greater impact on intellectual performance than lesions in orbitomedial areas[32]. However, Upton & Thompson[34] failed to find any consistent relationship between different lesion sites within the frontal lobes and specific patterns of cognitive impairment in a large sample of FLE subjects. Thus, different sites of epileptic foci may not have a substantial impact on cognitive performance. Possibly, the rapid propagation of seizure activity makes it irrelevant where in the frontal lobe seizures start.

We used a wide range of standard neuropsychological tests to assess intelligence, memory, attention and concept formation which are in frequent use for the presurgical evaluation of epilepsy subjects but failed to detect distinguishable neuropsychological profiles of FLE and TLE subjects. One might argue that although these tests are routinely used in neuropsychological assessment of epilepsy subjects they may not be efficient enough to detect the specific impairment of frontal lobe damage and more specific measures might be required. However, these tests are sensitive enough to reveal specific deficits, e.g. after surgery TLE subjects with left- sided lesions showed significantly more difficulties in verbal learning (*logical memory II* of the *WMS-R*) than subjects with right-sided lesions.

Extent of cognitive impairment in subjects with frontal lobe damage

In our first study we found that subjects with frontal lobe epilepsy scored significantly below the control group on almost all measures of intelligence, memory and attention that were used. Subjects with frontal lobe tumours obtained average performance IQs (85–115) and demonstrated a better verbal short time memory span (*digit span forward*) than FLE subjects but still performed below the healthy control group. Apart from these two measures both groups of subjects with frontal lobe damage did not significantly differ from each other on all other tasks. Both groups revealed the same globally impaired performance level compared to the healthy control group with pronounced deficits on measures of intelligence, memory and concentration. It seems that lesions to the frontal lobes disturb cognitive functions independently of the neurological cause. Seizure activity, probably with propagation to the contralateral hemisphere, might even be slightly more disruptive to speed and capacity of information processing than frontal lobe excisions after tumour removal.

Some of the cognitive measures that we found impaired in our FLE subjects (verbal short-term memory span, paired associative learning, concept formation) have been reported by other investigators to be disturbed in subjects with frontal pathology[17,27]. But overall intellectual and mnemonic performance on psychometric tests has in most studies been shown to be surprisingly well preserved after frontal lobe damage[17,35]. With regard to the specific sequelae of frontal lobe epilepsy full scale IQ scores and performances on memory tests have been within the normal range in the reported samples and deficits were only seen on measures of attention, motor and executive functions[6–8]. One possible explanation for the more generally impaired performance of our FLE subjects could be sought in a selection bias as our special epilepsy clinic is only attended by patients whose disease has been extremely difficult to manage and which may therefore present an especially impaired subgroup of FLE subjects. However, with regard to seizure characteristics (duration of illness, frequency of seizures) our FLE subjects compared well with other reported samples[7,8]. Therefore these variables may not be sufficient to account for the severity of cognitive deficits in our FLE sample.

The fact that long-standing epileptic activity can disrupt a great variety of cognitive functions, at least in a subgroup of severely affected subjects, may be explained by the sheer size of the frontal lobes, their functional diversity and numerous mutual connections to other brain areas. Pathological processes in the frontal lobes will therefore interfere with a great variety of cognitive functions. This process may be intensified by an assumed constant subclinical epileptic activity which has been shown to disrupt cognitive processes[36–39] and bilateral involvement through rapid propagation of seizures towards the contralateral hemisphere[15,40].

Influence of seizure history variables on cognitive functioning

Whereas in FLE subjects seizure history variables were not related to cognitive abilities, in TLE subjects age of onset as well as duration and severity of illness demonstrated significant relationships to a variety of neuropsychological test measures. The latter finding is consistent with the literature where seizure history variables have repeatedly been shown to influence cognitive performance in TLE subjects. Especially, age at onset of seizures has consistently proved to be a good predictor of later intellectual and mnemonic functioning[41–43] as subjects with early onset of seizures obtained lower adult test scores. For FLE subjects the relationship between seizure history and cognitive performance has only rarely been studied. Upton & Thompson[44] reported the influence of a set of seizure-related variables (aetiology, seizure spread, seizure frequency and duration of illness) on the neuropsychological performance of their large FLE sample. They found only limited support for the influence of seizure frequency and duration of illness on single variables. Aetiology and seizure spread seemed to have no consistent impact at all. In the same sample Upton & Thompson[45] tried to establish whether individuals with differing ages of epilepsy onset would be differentially impaired on certain cognitive tasks. The relationship could consistently be interpreted only for motor functions whereas on the measures of executive functioning, no consistent pattern emerged. The fact that we could not prove any relationship between seizure history variables and cognitive performance in our study may therefore be the result of our test selection which did not focus on motor functions. Furthermore, there were only four of our 16 FLE subjects who presented with epilepsy onset before the age of 20 years. We were thus unlikely to detect any difference in performance between early and late onset subjects.

Concluding remarks

In contrast to the global associative learning impairment of FLE subjects, TLE subjects in our investigation showed a selective deficit when learning pairs of emotional facial expressions. Significant differences between frontal and temporal epilepsy subjects on standard assessment measures occurred just on *digit span forward* when FLE subjects demonstrated a significantly reduced verbal short-term memory span compared to TLE subjects. Apart from these two measures the performance of FLE subjects could hardly be discriminated from that of TLE subjects as the latter showed a similarly reduced level of performance. The neuropsychological test measures which are routinely used for assessment of epilepsy subjects lack the specificity to detect differences between frontal and temporal lobe epilepsy. Highly specialized measures are necessary to reveal differences.

Subjects with frontal lobe epilepsy were globally impaired on a wide range of cognitive functions. It should therefore be noted that severe long-standing epilepsy in the frontal lobes can have a devastating effect on cognitive functioning at least in a subgroup of subjects whose seizures remain untreatable. One reason for this global impairment could be the propagation of seizure activity to the contralateral hemisphere and to distant brain regions, e.g. the temporal lobes.

In contrast with temporal lobe epilepsy seizure-history variables seem to have no detectable effect on cognitive functioning of FLE subjects.

REFERENCES

1. Helmstaedter, C., Pohl, C., Hufnagel, A. *et al.* Visual learning deficits in nonresected patients with right temporal lobe epilepsy. *Cortex* 1991; **27**: 547–555.
2. Jones-Gotman, M. Presurgical neuropsychological evaluation for localization and lateralization of seizure focus. In: *Epilepsy Surgery* (Ed. H. O. Lüders). New York, Raven, 1991: pp. 469–475.
3. Moore, P. and Baker, G. A. Validation of the Wechsler memory scale-revised in a sample of people with intractable temporal lobe epilepsy. *Epilepsia* 1996; **37**: 1215–1220.
4. Hermann, B. P., Seidenberg, M., Schoenfeld, J. *et al.* Neuropsychological characteristics of the syndrome of mesial temporal epilepsy. *Archives of Neurology* 1997; **54**: 369–376.
5. Ladavas, E., Carlo, U. and Provincialim, L. Hemisphere-dependent cognitive performance in epileptic patients. *Epilepsia* 1978; **20**: 493–502.
6. Delaney, R. C., Rosen, A. J., Mattson, R. H. *et al.* Memory function in focal epilepsy: a comparison of non-surgical, unilateral temporal lobe and frontal lobe samples. *Cortex* 1980; **16**: 103–117.
7. Helmstaedter, C., Kemper, B. and Elger, C. E. Neuropsychological aspects of frontal lobe epilepsy. *Neuropsychologia* 1996; **34**: 399–406.
8. Upton, D. and Thompson, P. J. General neuropsychological characteristics of frontal lobe epilepsy. *Epilepsy Research* 1996; **23**: 169–177.
9. Kemper, B., Helmstaedter, C. and Elger, C. E. Kognitive Profile von prächirurgischen Patienten mit Frontal- und Temporallappenepilepsie. In: *Epilepsie '91* (Ed. D. Scheffner). Reinbeck, Einhorn Presse Verlag, 1992: pp. 345–350.
10. Hermann, B. P., Wyler, A. R. and Richey, E. T. Wisconsin card sorting test performance in parients with complex partial seizures of temporal lobe origin. *Journal of Clinical and Experimental Neuropsychology* 1988; **10**: 467–476.
11. Horner, M. D., Flashman, L. A., Freides, D. *et al.* Temporal lobe epilepsy and performance on the Wisconsin card sorting test. *Journal of Clinical and Experimental Neuropsychology* 1996; **18**: 310–313.
12. Anderson, S. W., Damasio, H., Jones, R. D. *et al.* Wisconsin card sorting test performance as a measure of frontal lobe damage. *Journal of Clinical and Experimental Neuropsychology* 1991; **13**: 909–922.

13. Adam, C., Saint-Hilaire, J. M. and Richer, F. Temporal and spatial characteristics of intracerebral seizure propagation: predictive value in surgery for temporal lobe epilepsy. *Epilepsia* 1994; **35**: 1065–1072.
14. Emerson, R. G., Turner, C. A., Pedley, T. A. *et al.* Propagation patterns of temporal spikes. *Electroencephalography and Clinical Neurophysiology* 1995; **94**: 338–348.
15. Williamson, P. D. Frontal lobe seizures. Problems of diagnoses and classification. In: *Advances in Neurology, vol. 57, Frontal Lobe Seizures and Epilepsy* (Eds P. Chauvel, A. V. Delgado-Escueta, E. Halgren *et al.*). New York, Raven, 1992: pp. 289–309.
16. Goldman-Rakic, P. S., Selemon, L. D. and Schwartz, M. L. Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. *Neuroscience* 1984; **12**: 719–743.
17. Stuss, D. T., Eskes, G. A. and Foster, J. K. Experimental neuropsychological studies of frontal lobe function. In: *Handbook of Neuropsychology* Vol 9 (Eds F. Boller and J. Grafman). Amsterdam, Elsevier, 1994: pp. 149–185.
18. Weniger, G., Irle, E., Exner, C. *et al.* Defective conceptualization of emotional facial expressions during T2 signal enhancement of the right amygdala. *Neurocase* 1997; **3**: 259–266.
19. Boucsein, K., Weniger, G., Mursch, K. *et al.* Amygdala lesion in temporal lobe epilepsy subjects impairs associative learning of emotional facial expressions. *Neuropsychologia* 2001; **39**: 231–236.
20. Engel, J., Van Ness, P. C., Rasmussen, T. B. *et al.* Outcome with respect to epileptic seizures. In: *Surgical Treatment of the Epilepsies* (Ed. J. Engel). New York, Raven Press, 1993: pp. 609–621.
21. Dahl, G. *WIP. Reduzierter Wechsler-Intelligenztest.* Meisenheim am Glan, Verlag Anton Hain AG, 1972.
22. Tewes, U. *HAWIE-R—Hamburg-Wechsler-Intelligenztest für Erwachsene—Revision1991*. Bern, Huber, 1991.
23. Wechsler, D. *WMS-R—Wechsler Memory Scale—Revised*. San Antonio, Psychological Corporation, 1987.
24. Reitan, R. M. *Trail Making Test. Manual for Administration and Scoring*. South Tucson, AZ, Reitan Neuropsychological Laboratory, 1992.
25. Benton, A. L., Hamsher, K., Varney, N. R. *et al. Contributions to Neuropsychological Assessment*. New York, Oxford University Press, 1983.
26. Heaton, R. K. *Wisconsin Card Sorting Test Manual*. Odessa, Psychological Assessment Ressources, 1981.
27. Stuss, D. T. and Benson, D. F. *The Frontal Lobes*. New York, Raven Press, 1986.
28. Ekman, P. and Friesen, W. V. *Pictures of Facial Affect*. Palo Alto, Consulting Psychologists Press, 1976.
29. Petrides, M. Deficits on conditional associative-learning tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia* 1985; **23**: 601–614.
30. Gershberg, F. B. and Shimamura, A. P. Impaired use of organizational strategies in free recall following frontal lobe damage. *Neuropsychologia* 1995; **13**: 1305–1333.
31. Janowsky, J. S., Shimamura, A. P., Kritchevsky, M. *et al.* Cognitive impairment following frontal lobe damage and its relevance to human amnesia. *Behavioral Neuroscience* 1989; **103**: 548–560.
32. Rezai, K., Andreasen, N. C., Alliger, R. *et al.* The neuropsychology of the prefrontal cortex. *Archives of Neurology* 1993; **50**: 636–642.
33. Barcelo, F., Sanz, M., Molina, V. *et al.* The Wisconsin card sorting test and the assessment of frontal function: a validation study with event-related potentials. *Neuropsychologia* 1997; **35**: 399–408.
34. Upton, D. and Thompson, P. J. Epilepsy in the frontal lobes: neuropsychological characteristics. *Journal of Epilepsy* 1996; **9**: 215–222.
35. Irle, E., Exner, C., Thielen, C. *et al.* Obsessive-compulsive disorder and ventromedial frontal lesions: clinical and neuropsychological findings. *American Journal of Psychiatry* 1998; **155**: 255–263.
36. Wilkus, R. J. and Dodrille, C. B. Neuropsychological correlates of the electroencephalogram in epileptics: I. Topographic distribution and average rate of epileptiform activity. *Epilepsia* 1976; **17**: 89–100.
37. Aarts, J. H. P., Binnie, C. D., Smit, A. M. *et al.* Selective cognitive impairment during focal and generalized epileptiform activity. *Brain* 1984; **107**: 293–308.
38. Dodrill, C. B. Interictal cognitive aspects of epilepsy. *Epilepsia* 1992; **33** (suppl.): S7–S10.
39. Binnie, C. D. and Marston, D. Cognitive correlates of interictal discharges. *Epilepsia* 1992; **33** (suppl.): S11–S17.
40. Bancaud, J. and Talairach, J. Clinical semiology of frontal lobe seizures. In: *Advances in Neurology, vol. 57, Frontal Lobe Seizures and Epilepsy* (Eds P. Chauvel, A. V. Delgado-Escueta, E. Halgren *et al.*). New York, Raven, 1992: pp. 3–58.
41. Saykin, J. A., Gur, R. C., Sussman, N. M. *et al.* Memory deficits before and after temporal lobectomy: effects of laterality and age of onset. *Brain and Cognition* 1989; **9**: 191–200.
42. Dodrill, C. B. and Matthews, C. G. The role of neuropsychology in the assessment and treatment of persons with epilepsy. *American Psychologist* 1992; **47**: 1139–1142.
43. Baxendale, S. A., Paesschen, W. V., Thompson, P. J. *et al.* The relationship between quantitative MRI and neuropsychological functioning in temporal lobe epilepsy. *Epilepsia* 1998; **39**: 158–166.
44. Upton, D. and Thompson, P. Neuropsychological test performance in frontal-lobe epilepsy: the influence of aetiology, seizure type, seizure frequency and duration of disorder. *Seizure* 1997; **6**: 443–447.
45. Upton, D. and Thompson, P. J. Age at onset and neuropsychological function in frontal lobe epilepsy. *Epilepsia* 1997; **38**: 1103–1113.